EXHIBIT EE

EXHIBIT REDACTED IN ITS ENTIRETY

EXHIBIT FF

Aug 04 04 09:22a Kitty Huffman 540-786-0687 p.2

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/327,525	10/21/94	CHEE	M 16528X82

EXAMINER
REES, D

ART UNIT	PAPER NUMBER
1807	9

DATE MAILED: 12/19/95

18N1/1219

VERN NORVIEL
TOWNSEND AND TOWNSEND KHOURIE AND CREW
STEUART STREET TOWER
ONE MARKET PLAZA
SAN FRANCISCO CA 94105

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

10-23/95
5/18/95
3/23/95

☑ This application has been examined ☑ Responsive to communication filed on 5/24/95 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☑ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☑ Claims 1, 3-20, 45-59 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 1, 3-20, 45-59 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____, has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

PTOL-326 (Rev. 2/93)

EXAMINER'S ACTION

08327525

Part III DETAILED ACTION

Claim Rejections - 35 USC § 112

1. Claims 1,3-20, 45-59 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The following phrases render the claims vague and indefinite:

a) Claim 1 is indefinite in reciting "probe intensities being associated with a nucleic acid probe on a chip" in that it is not clear how the probe intensity is "associated" with the probe. For example, it is not clear whether an "intensity" value is an intrinsic property of each individual probe or if the "intensity" is actually a reflection of the extent of hybridization of probe molecules at a specific site on the chip. The claim might be amended to clarify this point.

b) Claim 1 is further indefinite in reciting "substantially proportional" in that it is not clear how "substantially" is defined.

c) Claim 1 is further indefinite is indefinite in reciting "said associated probe" in that it is the probe intensities which are said to "associated" with a nucleic acid probe; therefore this term lacks proper antecedent basis.

d) Claim 1 is further indefinite in reciting "calling said unknown base" in that it is unclear how "calling" is defined; i.e there appears to be a step missing. The comparing step provides a value with reference to standards? a blank? and the calling step is based on this value? Some recitation should be made in the claims of this intermediate step(s) as it appears to be an essential link between "comparing" and "calling".

e) Claim 4 is indefinite in reciting "calling said unknown base as being a base" in that it is unclear what the unknown base is specifically being "called". The claim might be amended to recite --calling said unknown base an A, T, C or G-- or alternatively --identifying an unknown base--. Further "said probe" lacks proper antecedent basis. It is additionally unclear what "a predetermined ratio value is" in that it is unclear what the reference point for this value is.

f) Claim 6 is indefinite in reciting the "step of sorting" said plurality of probe intensities in that it is not clear what the probe intensities are sorted into (i.e how does this differ from a comparison or the calling step?).

g) Claim 9 is indefinite in reciting "a wild type probe intensity" in that it is not clear how "wild-type" is defined in comparison with the "reference sequence" . Further the recitation of "each probe intensity of a probe" because it is unclear how a single probe can have more than one intensity (as implied by the use of the term "each").

h) Claims 9 and 10 are further indefinite in reciting "first ratios" and "second ratios" in that these ratios are not clearly defined with respect to probes and probe intensities. The problem seems to be mainly one of antecedent basis -it is not clear how "a probe" is to be distinguished from "each probe" in claim 10.

i) Claim 12 is indefinite in reciting "comparing said ratio of neighboring nucleic acid probes" in that it is not clear if the ratios of neighboring nucleic acid probes are compared to each other or to the reference sequence or both.

j) Claim 13 and 14 are indefinite in reciting "Probe intensities of a probe" in that it is not clear how "a" probe generates more than one intensity. It is further how probe intensities are "compared" to statistics and further what the outcome of this step is.

k) Claim 16 is indefinite in reciting "related probe intensities" in that it is not clear how the probes are related.

l) Claim 17 is indefinite in reciting "subtracting a background intensity" in that it is not clear how a background intensity is determined (before hybridization of the probes?).

m) Claim 45 is indefinite in reciting "the step of calling the unknown base". See paragraph 1d.

n) Claim 47 is indefinite in reciting "substantially proportional". See paragraph 1b.

o) Claim 49 is indefinite in reciting "calling step" and "predetermined ratio value". See paragraph 1d and 1e.

p) Claim 51 is indefinite in reciting "substantially proportional" (see paragraph 1b). The claim is further indefinite in reciting "to said associated nucleic acid probe hybridizing with a reference nucleic acid sequence" in that an associated nucleic acid probe hybridizing with a reference sequence has not been previously recited. Similarly the recitation of "said associated nucleic acid probe hybridizing with said sample sequence" lacks proper antecedent basis in this claim. Claim 51 is further indefinite in reciting "calling said unknown base according to results of said comparing step" (paragraph 1d).

q) Claim 52 is indefinite in reciting "calculating first ratios of a wild type probe intensity associated with a wild type probe" , in that it is not clear how a" wild-type probe is defined" (how is it distinguished from the reference sequence?). It is further unclear how "a probe" is distinguished from "each probe".

r) Claim 54 is indefinite in reciting "calling said unknown base". See paragraph 1d.

s) Claim 56 is further indefinite in reciting "comparing the ratio of neighboring nucleic acid probes" in that it is not clear what is being compared: the intensity ratios? And if the latter - of neighboring probes to each other? to reference probes?

t) Claim 57 is unclear in reciting "said plurality of probe intensities being associated with a nucleic acid probe in that it is unclear how a "plurality" of intensities are associate "a"

nucleic acid probe". The claim is further unclear in reciting "comparing at least one of said probe intensities with said statistics"-in that it is not clear exactly what is being compared or what the outcome of this comparison is that allows one to "call" an unknown base sequence.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order

for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 1,3-20, 45-59 are rejected under 35 U.S.C. § 103 as being unpatentable over Fodor et al. WO 92/10588 25 June 1992, in view of Weiss et al (USPAT 5470710, filed Oct 22, 1993)and Stockham et al. (USPAT 5273632, Dec 28, 1993).

Fodor et al. WO 92/10588 25 June 1992, teaches an SBH method wherein initial data resulting from a detection system is an array of data indicative of fluorescent intensity versus location of a substrate. Spurious data points are removed in the method to determine an average of data points. In general the data are fitted to a base curve and statistical measures are used to remove spurious data (page 17, lines 26-40). The detection method provides a positional localization of the region where hybridization takes place and upon having collected all the data indicating the subsequences present in the target sequence, this data may be aligned by overlap to reconstruct the entire sequence of the target (pages 35-36). Fodor also teaches that pixel density may be evaluated over a region to determine the locations and actual extent of a positive signal (this may be interpreted as performing a comparison of intensities in order to "call" a site) (page 76). Fodor teaches that although the method is most directly applicable to sequencing, the invention is also

applicable to fingerprinting, mapping and general screening of specific interactions. Thus the method of Fodor clearly suggests the comparison of hybridization of wild type sequences to mutant sequences or to reference sequences. The method of Fodor et al. differs from that of the present invention in that intensity ratios are not compared as a means on determining the identity of a base, rather it is the location of the signal which is called (although as noted above; distinguishing between different ratios of signal intensities is a part of the method of Fodor which allows one to determine a positive signal at any one site).

Weiss et al (USPAT 5470710, filed Oct 22, 1993) teaches a system which converts the signals obtained from a pattern of multiplex reaction products hybridized with fluorescent probes into a string of nucleotides corresponding to the nucleotide sequence (see abstract).The data acquired is interpreted by an algorithm that yields a "called sequence". Weiss teaches that a CCD snapshot of hybridization signals may be obtained and pixel values may be determined and averaged (column 14, lines 55-63). Ratios of signal intensities are determined using this system and statistics used to calculate standard deviations of sample intensities vs background signals. (see example 7).Further, Stockham et al. (USPAT 5273632, Dec 28, 1993) teaches a method of computerized analysis of the visual images of DNA sequence ladders. A digital lane signal is converted by Fourier transformation to a frequency spectrum. When all the lane signals

from a set of four lanes have been deconvolved using the same lifter function, the signals are normalized to each other (column 4, lines 56-70). A deconvolved signal is subjected to a preliminary peak detection step. A group of putative peaks is established by selecting all peaks which exceed a pre-established threshold intensity. The putative peaks include all peaks whose height (intensity) exceeds the value of the threshold function at their position, i.e a comparison of the ratios of intensities at a segment of a lane is used to determine an average peak height.Determination of threshold values is performed for each of the four lanes and a procedure for registering each of the four lanes is used which preferably places the peaks not only in the correct spatial order, but minimizes the variance of spacing. Preferably the alignment procedure uses high speed sorting across the lanes using a four lane interdependent adjustment of peak positions (columns 9-10). The nucleotide sequence is the correspondence between peak order among the different lanes and the lane associated with each peak, a step referred to as base calling. The methods of Weiss and Stockham do not set any limits on the numbers of ratios that can be determined using their computer system. Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time that the invention was made to use the computer algorithms of Stockham and Weiss to interpret the data inputted from the SBH system of Fodor, given that one could "call" a site

based on the intensity of a signal produced by an associated probe at that site and thus assign an identity to that site. It would be further well within the skill of the ordinary artisan, given the conventionality of standards or reference sequences to determine a predetermined ratio of signal intensities in order to assess whether a positive or negative signal is obtained at that site.

(It therefore appears that the issue of patentability in the present application resides in distinguishing over the "comparing" and "calling" processes of the computer algorithms of Weiss and Stockham and reciting this clearly in the claims).

3. The following references are additionally cited as relevant to programs designed to distinguish between ratios of intensities of light:

Rutenberg et al. (USPAT 4965725,Oct 23, 1993) teaches the use of a neural net system which is a commercially available statistical classifier which identifies a location of interest (in this example a cell) by measurement of integrated optical densities which are the sum of pixel grey values for the object corrected for optical errors. Based on data obtained from a

primary classifier, a secondary classifier is used to check specific areas of the specimen that are deemed to require further screening or classification. Such further examination may be effected by reliance on the already obtained digitized image data for the selected areas of a specimen or by taking additional data components (columns 3, lines 56-60, column 4, lines 7-18) Information within the system is stored in the strength of connections known as weights. In an asynchronous fashion, each processing element computes the sum of products of the weight of each input line multiplied by the signal level (usually 0 or 1) on that input line . If the sum of products exceeds a preset activation threshold, the output processing element is set to 1, if less, it is set to zero. Rutenberg also teaches that "a threelayer neural network can always find a representation that will map any input pattern to any desired output pattern".

Bacus (USPAT 4741043, April 26, 1988) teaches the use of a neural net system to determine the staining of DNA in cytological specimens. The system is calibrated for the optical density of an object , and incoming data may be converted to lookup tables in an imaging processing board so that the output shown optical density can be linearly added to proportionally reflect directly, in this instance the amounts of DNA (column 7, lines 4-11).

4. No claims are allowed.

5. Papers related to this application may be submitted to Group 1800 by facsimile transmission via the P.T.O. Fax Center located in Crystal Mall 1. The CM1 Fax Center number is (703) 305-7939. Please note that the faxing of such papers must conform with the notice to Comply published in the Official Gazette, 1096 OG 30 (Nov 15, 1989).

An inquiry regarding this communication should be directed to examiner Dianne Rees, Ph.D., whose telephone number is (703) 308-6565. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1156.

Calls of a general nature may be directed to the Group receptionist who may be reached at (703) 308-0196.

Dianne Rees
Dianne Rees

Dec 14, 1995

W. GARY JONES
SUPERVISORY PATENT EXAMINER
GROUP 1800
12/14/95

EXHIBIT GG

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/327,525	10/21/94	CHEE M.	16528X82

18M2/0709

VERN NORVIEL
TOWNSEND AND TOWNSEND KHOURIE AND CREW
STEUART STREET TOWER
ONE MARKET PLAZA
SAN FRANCISCO CA 94105

EXAMINER	
REES,	
ART UNIT	**PAPER NUMBER**
1807	24 13

DATE MAILED: 07/09/96

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

PTO-90C (REV. 2/95) T File Copy

Office Action Summary	Application No. 08/327,525	Applicant(s) CHEE ET AL.
	Examiner Dianne Rees	Group Art Unit 1807

☒ Responsive to communication(s) filed on *10/12/94, FAX OF 5/20/96*

☐ This action is FINAL.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *60-105* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *60-105* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *12*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

Part III DETAILED ACTION

The Applicant's arguments filed 5/20/96 have been thoroughly reviewed. Rejections and/or objections not reiterated from the previous office action are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated. They constitute the complete set being presently applied to the present application. Response to applicant's arguments follow.

Specification

1. The disclosure is objected to because of the following informalities:

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. 1.821 (a)(1) and (a)(2). However this application fails to comply with the requirements of 37 C.F.R. 1.821-25 for the reasons set forth on the Attached Notice to Comply with Requirements for Patent Applications And/or Amino Acid Sequence Disclosures.

APPLICANT IS GIVEN ONE MONTH FROM THE DATE OF THIS LETTER WITHIN WHICH TO COMPLY WITH THE SEQUENCE RULES, 37 C.F.R. 1.821-25. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 C.F.R. 1.821 (g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 C.F.R. 1.136. In No case may an applicant, extend the period for response beyond the six month statutory period. Direct the response to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the response..

Appropriate correction is required.

Claim Rejections - 35 USC § 101

2. 35 U.S.C. § 101 reads as follows:
"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent

therefore, subject to the conditions and requirements of this title".

Claims 60-105 are rejected under 35 U.S.C. § 101 ~~because the claims are drawn.~~ The claims are directed to a computer algorithm which is not applied in any manner to physical elements or process steps. See *In re Abele, 214 USPQ 682 (CCPA 1982)*. *See also Arrythymia v. Corazonix 22 USPQ 2d 1033 (Fed Cir 1992)* and *Gelnovatch 595 f. 2D AT 42, USPQ AT 145.*

The claim should be amended so that if viewed without the algorithm the process could stand alone. Further steps which have been determined by the courts to represent "insignificant post solution activity" (i.e the last step of a claim) are storing a pure number, displaying a pure number and calculating a pure number.

Claim Rejections - 35 USC § 112

3. Claims 60-105 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The following phrases render the claims vague and indefinite:

Claim 60 is indefinite in the recitation of "comparing said plurality of probe intensities" in that it is not clear what the

probe intensities are compared to (each other? a standard value?).

Claim 60 is also indefinite in the recitation of "identifying said unknown bases according to the results of the comparing step" in that it is not clear how one extrapolates from "comparing" to "identifying" (in general this is a problem with all the independent claims).

Claim 64 is indefinite in reciting "the step of sorting said plurality of probe intensities" -it is unclear if the claim refers to ranking the probe intensities in someway and if so by what criteria the probe intensities are sorted or ranked.

Claim 70 is indefinite in reciting " the step of identifying said unknown base according to said probe associated with a highest third ratio" in that it is not clear how the base is identified "according to said probe" (i.e what characteristic of the probe "identifies" the unknown base).

Claim 72 (see also claim 94) is indefinite in the recitation of "neighboring nucleic acid probes"; it is unclear whether "neighboring" defines probes that are immediately adjacent to a probe or encompasses a larger area. Clarification is requested.

Claim 81 (see also claim 92) is indefinite in reciting "identifying said unknown base according to a nucleic acid probe..." See above.

Claim 83 is indefinite in reciting "the step of sorting". See above.

Claims 60-105 are allowable over the prior art of record. The closest prior art of record is Weiss and Stockham who teach equations and formulas for sharpening signal peaks derived from electrophoretic migration patterns of nucleic acid ladders. Weiss and Stockham do not teach or fairly suggest a method if inputting probe intensities to identify an unknown base where the probe intensities indicate the extent of hybridization of probes differing by a single base and the same nucleic acid as recited in the base claim, claim 60.

No claims are allowed.

Papers related to this application may be submitted to Group 1800 by facsimile transmission via the P.T.O. Fax Center located in Crystal Mall 1. The CM1 Fax Center number is (703) 305-7401. Please note that the faxing of such papers must conform with the notice to Comply published in the Official Gazette, 1096 OG 30 (Nov 15, 1989).

An inquiry regarding this communication should be directed to examiner Dianne Rees, Ph.D., whose telephone number is (703) 308-6565. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1156.

Calls of a general nature may be directed to the Group receptionist who may be reached at (703) 308-0196.

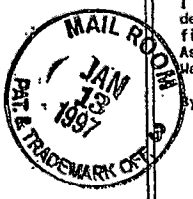
Dianne Rees
Dianne Rees

July 8, 1996

W. GARY JONES
SUPERVISORY PATENT EXAMINER
GROUP 1800
7/8/96

EXHIBIT HH

SL 1807



I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on 1-9-97

By Christine A. Bybee

PATENT

Attorney Docket No. 16528X-008200
(client file no. 1091)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

MARK S. CHEE ET AL.

Application No.: 08/327,525

Filed: October 21, 1994

For: COMPUTER-AIDED VISUALIZATION AND ANALYSIS SYSTEM FOR SEQUENCE EVALUATION

Examiner: D. Rees

Art Unit: 1807

#14
1-9-97

Petition to Extend Time Under 37 CFR § 1.136(a)

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Applicants petition the Commissioner of Patent and Trademarks to extend the time for response to the Office Action mailed July 9, 1996 for three months, from October 9, 1996 to January 9, 1997.

Please deduct $930 from the Deposit Account No. 20-1430. Please deduct any additional fees from or credit overpayment to the above Deposit Account. This Petition is submitted in triplicate.

Respectfully submitted,

Michael J. Ritter

Michael J. Ritter
Reg. No. 36,653

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, 8th Floor
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(415) 326-2400
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MJR:cab
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GR 1807

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on 1-9-97

By Christine A. Byfield

PATENT

Attorney Docket No. 16528X-008200
(client file no. 1091)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

MARK S. CHEE ET AL.

Application No.: 08/327,525

Filed: October 21, 1994

For: COMPUTER-AIDED VISUALIZATION AND ANALYSIS SYSTEM FOR SEQUENCE EVALUATION

Examiner: D. Rees

Art Unit: 1807

AMENDMENT

15 D 1807 aug 8 1-9-97

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

In response to the Office Action mailed July 9, 1996, for which a petition for an extension of time is enclosed, please amend this application as follows.

IN THE CLAIMS:

For the Examiner's convenience, all claims pending are shown below. Claims that have not been amended herein are shown in small print.

Please cancel claims 72 and 94 without prejudice and amend claims 60, 62, 64, 70, 72, 81, 83, 88, 92, 94, and 99 as follows.

1-59. ~~CANCELED~~ Done by C.

60. (Amended) In a computer system, a method of identifying an unknown base in a sample nucleic acid sequence, said method comprising the steps of:

imputing a plurality of probe intensities for a plurality of nucleic acid probes, each probe intensity indicating an extent of hybridization of a nucleic acid probe with at least one nucleic acid sequence including said sample sequence, and each nucleic acid probe differing from each other by at least a single base;

said computer system comparing said plurality of probe intensities to each other; and

said computer system generating a base call identifying said unknown base according to results of said comparing step.

61. The method of claim 60, wherein said comparing step includes the step of said computer system calculating a ratio of a higher probe intensity to a lower probe intensity.

62. (Amended) The method of claim 61, wherein said generating [identifying] step includes the step of identifying said unknown base according to a nucleic acid probe having said higher probe intensity if said ratio is greater than a predetermined ratio value.

63. The method of claim 62, wherein said predetermined ratio value is approximately 1.2.

64. (Amended) The method of claim 60, further comprising the step of sorting said plurality of probe intensities by intensity before said comparing step.

65. The method of claim 60, wherein said at least one sequence includes a reference sequence.

66. The method of claim 65, wherein said comparing step includes the step of said computer system comparing probe intensities of a probe hybridizing with said sample sequence to said probe hybridizing with said reference sequence.

67. The method of claim 65, wherein said comparing step includes the step of calculating first ratios of a wild-type probe intensity to each probe intensity of probes hybridizing with said reference sequence, wherein

said wild-type probe intensity indicates an extent of hybridization of a complementary probe with said reference sequence.

68. The method of claim 67, wherein said comparing step includes the step of calculating second ratios of the highest probe intensity of a probe hybridizing with said sample sequence to each probe intensity of probes hybridizing with said sample sequence.

69. The method of claim 68, wherein said comparing step includes the step of calculating third ratios of said first ratios to said second ratios.

70. (Amended) The method of claim 69, wherein said generating [identifying] step includes the step of identifying said unknown base according to a base of said probe associated with a highest third ratio.

71. The method of claim 68, wherein said comparing step includes the step of calculating a ratio of a highest probe intensity of a probe hybridizing with said reference sequence to a highest intensity of a probe hybridizing with said sample sequence.

72. --CANCELED--

73. The method of claim 65, wherein probe intensities of probes hybridizing with said reference sequence are from a plurality of experiments.

74. The method of claim 73, wherein said comparing step includes the step of said computer system comparing probe intensities of probes hybridizing with said sample sequence to statistics about said plurality of experiments.

75. The method of claim 74, wherein said statistics include a mean and standard deviation.

76. The method of claim 73, further comprising the step of normalizing said plurality of probe intensities by dividing each probe intensity by a sum of related probe intensities, wherein related probe intensities are from probes that differ by a single base.

77. The method of claim 60, further comprising the step of subtracting a background intensity from each of said plurality of probe intensities.

78. The method of claim 60, further comprising the step of setting a probe intensity equal to a positive number if said probe intensity is less than or equal to zero.

79. The method of claim 60, further comprising the step of indicating said unknown base is unable to be identified if said plurality of probe intensities have insufficient intensity to identify said unknown base.

80. The method of claim 60, wherein said unknown base is identified as being A, C, G, or T.

81. (Amended) In a computer system, a method of identifying an unknown base in a sample nucleic acid sequence, said method comprising the steps of:

imputing a plurality of probe intensities for a plurality of nucleic acid probes, each probe intensity indicating an extent of hybridization of a nucleic acid probe with said sample sequence, and each nucleic acid probe differing from each other by at least a single base;

said computer system calculating a ratio of a higher probe intensity to a lower probe intensity; and

said computer system generating a base call identifying said unknown base according to a base of a nucleic acid probe having said higher probe intensity if said ratio is greater than a predetermined ratio value.

82. The method of claim 81, wherein said predetermined ratio value is approximately 1.2.

83. (Amended) The method of claim 81, further comprising the step of sorting said plurality of probe intensities by intensity before said comparing step.

84. The method of claim 81, further comprising the step of subtracting a background intensity from each of said plurality of probe intensities.

85. The method of claim 81, further comprising the step of setting a probe intensity equal to a positive number if said probe intensity is less than or equal to zero.

86. The method of claim 81, further comprising the step of indicating said unknown base is unable to be identified if said plurality of probe intensities have insufficient intensity to identify said unknown base.

87. The method of claim 81, wherein said unknown base is identified as being A, C, G, or T.

88. (Amended) In a computer system, a method of identifying an unknown base in a sample nucleic acid sequence, said method comprising the steps of:

imputing a first set of probe intensities, each probe intensity in said first set indicating an extent of hybridization of a nucleic acid probe with a reference nucleic acid sequence, and each nucleic acid probe differing from each other by at least a single base;

imputing a second set of probe intensities, each probe intensity in said second set indicating an extent of hybridization of a nucleic acid probe with said sample sequence, and each nucleic acid probe differing from each other by at least a single base;

said computer system comparing at least one of said probe intensities in said first set and at least one of said probe intensities in said second set; and

said computer system generating a base call identifying said unknown base according to results of said comparing step.

89. The method of claim 88, wherein said comparing step includes the step of calculating first ratios of a wild-type probe intensity to each probe intensity of probes hybridizing with said reference sequence, wherein said wild-type probe intensity indicates an extent of hybridization of a complementary probe with said reference sequence.

90. The method of claim 89, wherein said comparing step includes the step of calculating second ratios of the highest probe intensity of probes hybridizing with said sample sequence to each probe intensity of a probe hybridizing with said sample sequence.

91. The method of claim 90, wherein said comparing step further includes the step of calculating third ratios of said first ratios to said second ratios.

92. (Amended) The method of claim 91, wherein said generating [identifying] step includes the step of identifying said unknown base according to a base of said probe associated with a highest third ratio.

93. The method of claim 88, wherein said comparing step includes the step of calculating a ratio of a highest probe intensity in said first set to a highest intensity in said second set.

94. --CANCELED--

95. The method of claim 88, further comprising the step of subtracting a background intensity from each of said plurality of probe intensities.

96. The method of claim 88, further comprising the step of setting a probe intensity equal to a positive number if said probe intensity is less than or equal to zero.

97. The method of claim 88, further comprising the step of indicating said unknown base is unable to be identified if said plurality of probe intensities have insufficient intensity to identify said unknown base.

98. The method of claim 88, wherein said unknown base is identified as being A, C, G, or T.

99. (Amended) In a computer system, a method of identifying an unknown base in a sample nucleic acid sequence, said method comprising the steps of:

imputing statistics about a plurality of experiments, each of said experiments producing probe intensities, each probe intensity indicating an extent of hybridization of a nucleic acid probe with a reference nucleic acid sequence, and each nucleic acid probe differing from each other by at least a single base;

imputing a plurality of probe intensities, each probe intensity indicating an extent of hybridization of a nucleic acid

probe with said sample sequence, and each nucleic acid probe differing from each other by at least a single base;

said computer system comparing at least one of said plurality of probe intensities with said statistics; and

said computer system generating a base call identifying said unknown base according to results of said comparing step.

100. The method of claim 99, wherein said statistics include a mean and standard deviation.

101. The method of claim 99, further comprising the step of normalizing said plurality of probe intensities by dividing each probe intensity by a sum of related probe intensities, wherein related probe intensities are from probes that differ by a single base.

102. The method of claim 99, further comprising the step of subtracting a background intensity from each of said plurality of probe intensities.

103. The method of claim 99, further comprising the step of setting a probe intensity equal to a positive number if said probe intensity is less than or equal to zero.

104. The method of claim 99, further comprising the step of indicating said unknown base is unable to be identified if said plurality of probe intensities have insufficient intensity to identify said unknown base.

105. The method of claim 99, wherein said unknown base is identified as being A, C, G, or T.

Please add new claims 106-117 as follows.

106. The method of claim 60, wherein the plurality of nucleic acid probes are in an array of probes.

107. The method of claim 60, wherein the plurality of probe intensities are fluorescent intensities.

108. A computer program product that identifies an unknown base in a sample nucleic acid sequence, comprising:

computer code that receives a plurality of probe intensities for a plurality of nucleic acid probes, each probe intensity indicating an extent of hybridization of a nucleic acid probe with at least one nucleic acid sequence including said sample sequence, and each nucleic acid probe differing from each other by at least a single base;

computer code that performs a comparison of said plurality of probe intensities to each other;

computer code that generates a base call identifying said unknown base according to results of said comparison; and

a computer readable medium that stores said computer codes.

109. A computer program product that identifies an unknown base in a sample nucleic acid sequence, comprising:

computer code that receives a plurality of probe intensities for a plurality of nucleic acid probes, each probe intensity indicating an extent of hybridization of a nucleic acid probe with said sample sequence, and each nucleic acid probe differing from each other by at least a single base;

computer code that calculates a ratio of a higher probe intensity to a lower probe intensity;

computer code that generates a base call identifying said unknown base according to a base of a nucleic acid probe having said higher probe intensity if said ratio is greater than a predetermined ratio value; and

a computer readable medium that stores said computer codes.

110. A computer program product that identifies an unknown base in a sample nucleic acid sequence, comprising:

computer code that receives a first set of probe intensities, each probe intensity in said first set indicating an extent of hybridization of a nucleic acid probe with a reference nucleic acid sequence, and each nucleic acid probe differing from each other by at least a single base;

computer code that receives a second set of probe intensities, each probe intensity in said second set indicating an extent of hybridization of a nucleic acid probe with said sample sequence, and each nucleic acid probe differing from each other by at least a single base;

computer code that performs a comparison of at least one of said probe intensities in said first set and at least one of said probe intensities in said second set;

computer code that generates a base call identifying said unknown base according to results of said comparison; and

a computer readable medium that stores said computer codes.

111. A computer program product that identifies an unknown base in a sample nucleic acid sequence, comprising:

computer code that receives statistics about a plurality of experiments, each of said experiments producing probe intensities, each probe intensity indicating an extent of hybridization of a nucleic acid probe with a reference nucleic acid sequence, and each nucleic acid probe differing from each other by at least a single base;

computer code that receives a plurality of probe intensities, each probe intensity indicating an extent of hybridization of a nucleic acid probe with said sample sequence, and each nucleic acid probe differing from each other by at least a single base;

computer code that performs a comparison of at least one of said plurality of probe intensities with said statistics;

computer code that generates a base call identifying said unknown base according to results of said comparison; and

a computer readable medium that stores said computer codes.

112. A system that identifies an unknown base in a sample nucleic acid sequence, comprising:

a processor; and

a computer readable medium coupled to said processor for storing a computer program comprising:

computer code that receives a plurality of probe intensities for a plurality of nucleic acid probes, each probe intensity indicating an extent of hybridization of a nucleic acid probe with at least one nucleic acid sequence including said sample sequence, and each nucleic acid probe differing from each other by at least a single base;

computer code that performs a comparison of said plurality of probe intensities to each other; and

computer code that generates a base call identifying said unknown base according to results of said comparison.

113. A system that identifies an unknown base in a sample nucleic acid sequence, comprising:

a processor; and

a computer readable medium coupled to said processor for storing a computer program comprising:

computer code that receives a plurality of probe intensities for a plurality of nucleic acid probes, each probe intensity indicating an extent of hybridization of a nucleic acid probe with said sample sequence, and each nucleic acid probe differing from each other by at least a single base;

computer code that calculates a ratio of a higher probe intensity to a lower probe intensity; and

computer code that generates a base call identifying said unknown base according to a base of a nucleic acid probe having said higher probe intensity if said ratio is greater than a predetermined ratio value.

114. A system that identifies an unknown base in a sample nucleic acid sequence, comprising:

a processor; and

a computer readable medium coupled to said processor for storing a computer program comprising:

computer code that receives a first set of probe intensities, each probe intensity in said first set indicating an

extent of hybridization of a nucleic acid probe with a reference nucleic acid sequence, and each nucleic acid probe differing from each other by at least a single base;

computer code that receives a second set of probe intensities, each probe intensity in said second set indicating an extent of hybridization of a nucleic acid probe with said sample sequence, and each nucleic acid probe differing from each other by at least a single base;

computer code that performs a comparison of at least one of said probe intensities in said first set and at least one of said probe intensities in said second set; and

computer code that generates a base call identifying said unknown base according to results of said comparison.

115. A system that identifies an unknown base in a sample nucleic acid sequence, comprising:

a processor; and

a computer readable medium coupled to said processor for storing a computer program comprising:

computer code that receives statistics about a plurality of experiments, each of said experiments producing probe intensities, each probe intensity indicating an extent of hybridization of a nucleic acid probe with a reference nucleic acid sequence, and each nucleic acid probe differing from each other by at least a single base;

computer code that receives a plurality of probe intensities, each probe intensity indicating an extent of hybridization of a nucleic acid probe with said sample sequence, and each nucleic acid probe differing from each other by at least a single base;

computer code that performs a comparison of at least one of said plurality of probe intensities with said statistics; and

computer code that generates a base call identifying said unknown base according to results of said comparison.--

116. A system according to claims 112, 113, 114, or 115, wherein the plurality of nucleic acid probes are in an array of probes.

117. A system according to claims 112, 113, 114, or 115, wherein the plurality of probe intensities are fluorescent intensities.--

REMARKS

Claims 60-71, 73-93, and 95-117 are pending in the subject application. Applicants canceled claims 72 and 94 without prejudice and reserve all right to pursue these or other claims in another application. Claims 106-117 were added by this Amendment. In light of the amendments and following remarks, Applicants believe all claims now pending are in condition for allowance.

The Examiner indicated that claims 60-105 were allowable over the cited art, however, the disclosure was objected to because the Sequence Listing did not conform to 37 C.F.R. §§ 1.821-25. Additionally, claims 60-105 were rejected under 35 U.S.C. § 101 as being directed at non-statutory subject matter and under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject invention.

The Sequence Listing

The Office Action mailed July 9, 1996 did not include a Notice to Comply. Applicants telephoned the Examiner on July 17, 1996 to inform her that the Notice had not been received. Applicants appreciate the Examiner's diligence in faxing the Sequence Verification Report (enclosed) to the undersigned's attention on August 22, 1996.

Applicants corrected the Sequence Listing to remedy errors specified in the faxed Report. The corrections include replacing each occurrence of 'X' in the Sequence Listing with an 'N' (both were utilized in the specification to indicate an

ambiguous base; see page 11, lines 38-42, of the specification). Applicants submit herewith a corrected Sequence Listing and diskette including the Sequence Listing in computer readable form.

The Office Action stated that the Notice to Comply had a shortened statutory period for response of one month from the mailing date; however, Applicants never received the Notice. In a telephone conversation with the Examiner on December 9, 1996, the Examiner indicated that it would be permissible to file the new Sequence Listing with this Amendment along with the requisite petition for three months extension of time. Should any other fees be required, Applicants authorize any other fees to be charged to Deposit Account No. 20-1430.

The Invention

The Examiner acknowledges that the present invention provides innovative computer-aided methods that are not disclosed or suggested in the prior art for identifying unknown bases in nucleic acids. However, the Examiner rejected the claims under § 101 and § 112, second paragraph. Applicants have amended the claims to overcome the rejections and will discuss each of the Examiner's specific rejections below.

The § 101 Rejection

The Examiner rejected claims 60-105 under 35 U.S.C. § 101 as being directed to non-statutory subject matter. More specifically, the Examiner stated that the claims are directed to a computer algorithm which is not applied to physical elements or process steps. Applicants respectfully disagree. The claims recite computer-aided processes which analyze probe intensities indicative of the extent of hybridization of the nucleic acid probes and the sample sequence. The extent of hybridization is indeed a physical quantity just as are electrocardiograph signals (see Arrhythmia Research Tech. v. Corazonix Corp., 958 F2d 1053, 22 USPQ2d 1033 (Fed. Cir. 1992)). In order to more clearly recite the invention, Applicants amended the independent claims to recite that "said computer system generat[es] a base call"

that identifies an unknown base. Therefore, the claims recite statutory computer-aided processes of receiving probe intensities indicative of hybridization with a sample sequence and generating a base call of an unknown base in the sample sequence.

The Examiner suggested that the claims "should be amended so that if viewed without the algorithm the process would stand alone." Applicants understand the Examiner to say that the claims should recite statutory subject matter in the abstract, without consideration of an algorithm or computer. For example, processes of curing synthetic rubber are statutory subject matter so a process of curing synthetic rubber that utilizes a computer is also statutory subject matter (see Diamond v. Diehr, 450 US 175, 209 USPQ 1 (1981)). Applicants submit that processes for identifying unknown bases in sample nucleic acids are statutory subject matter so the recited computer-aided processes are also statutory subject matter.

Applicants have reviewed the Examination Guidelines for Computer-Related Inventions in § 2106 of the MPEP (see, e.g., the section entitled "Manipulation of Data Representing Physical Objects or Activities" in MPEP § 2106(IV)(B)(2)(b)(i)). Applicants fully believe that the pending claims are directed to statutory subject matter. Applicants invite the Examiner to telephone the undersigned if a telephone discussion would facilitate prosecution of the subject application.

The § 112, Second Paragraph, Rejections

The Examiner rejected claims 60-105 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject invention. With regard to claim 60, the Examiner indicated it is not clear to what the probe intensities are compared. Applicants amended claim 60 to recited that the probe intensities are compared to each other (see, e.g., Figs. 3, 4A and 5A). Accordingly, the rejection is overcome.

Additionally, the Examiner stated that claim 60 is indefinite in that it is not clear how one extrapolates from "comparing" to "identifying." Applicants respectfully submit

that, when read in light of the specification as the case law requires, the claims are not unclear. Applicants' specification provides full detail on possible "comparing" and "generating" (as amended) steps. For example, the highest probe intensity may be compared to the next highest probe intensity to generate a ratio. If this ratio is greater than a predetermined ratio cutoff, the unknown base will be called according to (e.g., complementary to) a base in the probe with the highest intensity (see page 14, lines 23-34). Many of the dependent claims recite further details on these steps (see, e.g., claims 61-63). As Applicants' specification provides ample description of exemplary ways that the present invention may be performed, Applicants request that this rejection be withdrawn.

With regard to claim 64, the Examiner indicated it is unclear how the probe intensities are sorted. Applicants amended claim 64 to recite that the probe intensities are sorted "by intensity" (see, e.g., page 14, line 17). Accordingly, the rejection is overcome.

The Examiner indicated that in claim 70 it is unclear what characteristic of the probe "identifies" the unknown base. As described in the specification, the nucleic acid probes are generally complementary to the sample sequence in order to allow for hybridization between the probes and the sample sequence. Applicants amended claim 70 to recite that the unknown base is identified according to "a base" of a probe with a highest ratio (see page 24, lines 5-10). Accordingly, the rejection is overcome.

The Examiner rejected claims 72 and 94. In a sincere effort to expedite prosecution. Applicants canceled these claims rendering the rejections moot.

The Examiner rejected claims 81, 83, and 92 for the same reasons as claims discussed above. Applicants amended these and other claims in the manner discussed to overcome the rejections. Therefore, Applicants have addressed all the § 112, second paragraph, rejections and respectfully request that these rejections be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at (415) 326-2400.

Respectfully submitted,

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EXHIBIT II

EXHIBIT REDACTED IN ITS ENTIRETY

CERTIFICATE OF SERVICE

I hereby certify that on the 17th day of April, 2006, I caused to be electronically filed the foregoing document, **PUBLIC VERSION OF APPENDIX TO ILLUMINA, INC.'S OPENING MARKMAN BRIEF – VOLUME 3 OF 3,** with the Clerk of the Court using CM/ECF which will send notification of such filing to the following:

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Additionally, I hereby certify that on the 17th day of April, 2006, the foregoing document was served on the following via email:

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